Journal of Critical Reviews

ISSN- 2394-5125 Vol 7, Issue 13, 2020

INVESTIGATING THE RAPID METHOD OF DIAGNOSING MENINGITIS IN HUMANS

Shaqayeq Khosravi [1], Seyedeh Mahsa Mahmoudinezhad Dezfouli [1*]

[1.] Emergency Medicine Management Research Center, Iran University of Medical Sciences, Aliasghar children Hospital, Tehran, Iran

***Corresponding author: Seyedeh Mahsa Mahmoudinezhad Dezfouli, Emergency Medicine Management Research Center, Iran University of Medical Sciences, Aliasghar children Hospital, Tehran, Iran**

Email: mahmoudinejad.m@iums.ac.ir

Received: 10.04.2020 ***Revised: 11.05.2020*** ***Accepted: 07.06.2020***

Abstract

Meningitis is a disease that can be caused by a variety of factors such as bacteria, viruses, or funguses. Occasionally, in the dangerous type of meningitis caused by bacteria, meningitis passes through the mucous membrane, enters the bloodstream, and causes various severe clinical syndromes, the most common of which is acute meningitis. Complications include hearing loss, vision loss, and memory impairments or even death. Despite bacterial treatment, at least 10% of patients, most of whom are young children, die within 1 or 2 days of onset, and 10 -20% of survivors face significant neurological consequences. Patients with meningitis should be identified immediately and the cause of the disease should be correctly identified. Various methods are used, including biochemical blood tests and spinal cord fluid analysis. This review article will first examine the bacteria that cause meningitis in humans and then samples of cerebrospinal fluid and detection will be discussed.

Keywords: Meningitis, cerebrospinal fluid, LP, risk factor score.

DOI: http://dx.doi.org/10.31838/jcr.07.13.46

INTRODUCTION

Meningitis is a disease in which the membrane covering the brain and spinal cord become inflamed. This inflammation is caused by infection of the tissue around the brain and spinal cord by bacterial or viral agents and causes symptoms such as headache, fever and neck stiffness. 90% of the disease occurs in childhood and can be associated with children for many years. Meningitis is one of the deadliest and most highly morbid diseases in children. The reason for the greater involvement of children with this disease can be considered the weakness of their immune system compared to adults [1, 2].

It should be noted that meningitis does not cause additional involvement in the central nervous system like diseases such as encephalitis and myelitis. Meningitis is one of the diseases that has relatively high rates of death and complications. The incidence of meningitis in the world is estimated at 20 per 100,000 people per year. The most obvious symptom is a headache, but most children do not have a specific symptom or have a fever just before the onset of systemic manifestations. Also in the United States, the disease kills 2,000 people a year. Naturally, the mortality rate due to meningitis is higher in less developed countries [3, 4]. Meningitis can be caused by viruses, bacterial infections, rickettsiae, spirochetes, protozoa, fungi, and some intracranial drugs and tumors [2].

Most patients with untreated viral meningitis recover in a few weeks, however meningitis can be life-threatening and require immediate treatment. If bacterial meningitis is not treated quickly, it can cause brain problems such as deafness, blindness, neurological disorders, decreased level of consciousness, paralysis and even death of the patient [5, 6].

Early symptoms of viral meningitis and bacterial meningitis can be similar. However, the symptoms of this bacterial disease are usually more severe and can vary depending on the patient's age. Clinical symptoms in patients with meningitis progress within a few hours to a few days or over weeks to months [1]. Viral infections are more common with meningitis, but since bacterial infections can be life-threatening, it is more important to identify the cause of the disease. Early diagnosis and treatment of meningitis is vastly important in helping patients [7].

Meningitis

Mortality rate in viral meningitis is very low and most patients recover, but in bacterial meningitis, depending on the type of bacterium, it could kill 10% to 25% if left without appropriate treatment. Also, depending on the patient's age, underlying disease, and surgery on the nervous system, different bacteria cause different symptoms in the patient. Bacterial meningitis is contagious and is caused by a specific bacterial infection that could be fatal if left untreated.

Symptoms of bacterial meningitis are sudden and include headache, sore throat, runny nose, cough, and conjunctivitis. Symptoms such as nausea, vomiting, fever and chills, arthralgia and myalgia also show up when the disease enters its more severe phase. Fever was severe in these patients and was reported to be between 39 and 41 degrees [1, 2].

Bacteria enter the bloodstream and travel to the brain and spinal cord, causing acute bacterial meningitis. Also, possibly there is the risk of infection in the ear or sinuses, trauma or rarely after surgery, bacteria can directly invade the meninges of the brain. The most important bacteria that cause meningitis are Escherichia coli, Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis and Listeria. Observations show that more than 80% of the disease is caused by Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis [8]. In another decade-long study of workers in Birmingham, the bacteria Neisseria meningitidis were identified as the most common pathogen causing meningitis, Haemophilus influenzae as the second most common cause, and pneumococcus as the third most common cause of meningitis [9].

A report by Ali Akbar Heydari et al., at Imam Reza Hospital, Mashhad, Iran, found that if meningitis lasted more than a week and a cerebrospinal fluid test showed a decrease in sugar levels and an increase in protein levels, it could be due to tuberculosis and Brucellosis and it should also be considered [10].

Tuberculous meningitis is the most dangerous extrapulmonary form of tuberculosis and it could be seen in 7 to 12% of TB patients in developing countries. In most cases, this meningitis is chronic[11] . If left untreated, the mortality rate in these patients

is high, in addition in 20 to 25 percent of patients who were treated late, neurological side effects have been observed [12, 13]. Common bacteriological methods are not suitable for the correct diagnosis of this disease, and usually false-negative results are obtained from these methods. However, tuberculous meningitis is one of the most urgent infectious diseases and requires immediate and early diagnosis [14].

Streptococcus pneumoniae (pneumococcus)

Streptococcus pneumoniae is the most common cause of meningitis in infants, children, and adults. Today, despite the significant advances in treatment and vaccination, mortality rate from pneumococcal meningitis is 16 to 37 percent, and neurological complications including hearing loss, focal neurological impairment, and cognitive impairment are estimated to occur in 30 to 52 percent of residual patients [15, 16].

The human nasopharynx is the main reservoir of pneumococcus, and bacteria are usually found there without symptoms. The highest rate of pneumococcus among children is 37 percent and may increase to 58 percent in crowded places such as day care centers. In adults, overcrowding may also lead to an increase, for example in hospitals, long-term care centers, shelters and prisons, the rate of bacterial carriers were reported to be up to 40% [17, 18].

The bacterium is mainly transmitted through coughing and sneezing. In patients with diseases such as sickle cell disease, multiple myeloma, hypogammaglobulinemia, alcoholism, chronic liver or kidney disease, malignancy, thalassemia major, diabetes mellitus, basal cell skull fractures with cerebrospinal fluid leakage, and also in children using cochlear implants, Immune system suppressants, diabetes and HIV infection, pneumococcal meningitis could occur possibly. [7, 19, 20].

Laminin appears to be involved in the binding of endothelial microvascular cells in the brain. In a study of mice, Pneumococcal surface Protein C (PspC) mutations reduced the frequency of pneumococcal meningitis. These results suggest that the interaction between laminin and pneumococcal PspC plays an important role in the intracellular transfer of pneumococci through the blood brain barrier [21].

Escherichia coli

Despite therapeutic advances against microbes and supportive cares, meningitis caused by gram-negative bacilli is still one of the leading causes of death worldwide. The mortality rate is between 15 and 40 percent, and approximately 50 percent of the survivors have neurological complications [22].

Escherichia coli is the most common gram-negative organism that causes meningitis, especially in infancy. Most cases of Escherichia coli meningitis are spread by blood transfusions [23]. Diabetes and surgery are predisposing factors for Escherichia coli meningitis [24, 25]. This type of meningitis is also more likely to occur after severe infections caused by Strongyloides stercoralis in infants, the elderly, people with weakened immune systems, and patients with gram-negative septicemia. Unfortunately, the findings of a 2005 study by Yang et al. Show that the negative gram-negative meningitis caused by Escherichia coli is greatly increasing [25].

Escherichia coli infiltration of the blood-brain barrier is an important factor in the progression of meningitis. Bacteria can cross the blood-brain barrier intracellularly, extracellularly, or through infected phagocytic cells. Successful passage of the bacterium requires a high level of bacterial concentration, and in addition binding and attacking Human Brain Microvascular Endothelial Cells (HBMEC). After the Escherichia coli bacterium penetrates the blood-brain barrier, bacterial meningitis is characterized by meninges inflammation, which occurs in response to bacteria and bacterial products, resulting in the release of cytokines and chemokines, as well as pathophysiological changes, including leukocyte infiltration and dysfunction of the blood-brain barrier [26, 27]. Studies have shown that the mechanisms involved in microbial invasion into the blood-brain barrier are different from the response to meningitis-causing pathogens in the release of cytokines and chemokines. For example, interleukin secretion (IL-8) occurs in Escherichia coli response in HBMEC, but would not occur in non-cerebral endothelial cells [28, 29].

It should be noted that the lack of specific and appropriate antibiotic intake in gram-negative meningitis is always associated with mortality in patients. Studies have shown that the mortality rate with specific antibiotic intake is between 28 and 40 percent. Despite the high mortality rate with timely diagnosis and appropriate treatment, patient mortality could be prevented. Predisposing factors for Escherichia coli meningitis include infectious shock, decreased level of consciousness during hospitalization, diffuse intravascular coagulation, hyperglycemic coma, high lactate levels in CSF, and leukocytosis [30, 31].

Meningococcus

In 1987, Weichselbaum was the first person to detect and diagnose meningococcus in cerebrospinal fluid (CSF) in a patient with meningitis [32]. The human species are the only natural host of meningococcus. Meningococcus has created several mechanisms that are able to transmit, adapt, and colonize most of the mucosal surfaces of the human upper respiratory tract. Some meningococcal colon groups also have the capacity to cause invasive disease. These bacteria usually cause upper respiratory infections and are highly contagious infections that mainly affect adolescents and adults [33, 32].

The invasive factors of meningococci are due to the interaction of microbial agents affecting the severity of the organism, the environmental conditions that facilitate exposure to bacteria, and the host susceptibility factors to bacteria, invasion and survival. Meningococcal disease is associated with significant complications such as loss of limbs, hearing loss, cognitive impairment, visual impairment, academic problems, growth retardation, motor nerve defects, seizure disorders and behavioral problems [33]. Treatment for meningococcal disease includes serum therapy and sulfonamides introduced in 1937. The advent of sulfonamide resistance in the 1960s created the first vaccines against meningococci [34, 35].

Listeria

Listeria is a gram-positive bacillus found mainly in contaminated food, and after the outbreak of leukemia in the 1980s, Listeria monocytogenes is the third most common cause of bacterial meningitis [36]. Meningitis caused by Listeria has been described as a disease in immunocompromised patients and the elderly with a high mortality rate. As many studies have shown, the incidence of healthy children with this disease is less than 6% [37].

In patients with meningitis infected with Listeria fever, neck stiffness and altered mood were reported in 43% of patients, and in almost all patients at least 2 of the 4 symptoms of headache, fever, neck stiffness, and altered mood were observed. [38]. Also, many adults with Listeria meningitis had atypical CSF findings, and only 23% of patients did not have any bacterial-based CSF findings [37]. For the treatment of suspected bacterial meningitis, amoxicillin-based antimicrobial therapy is recommended for patients over the age of 50 or with risk factors to cover Listeria, as the bacterium is resistant to cephalosporins [39].

Haemophilus influenzae

The bacterium Haemophilus influenzae lives in the nasopharynx and is usually harmless. However, bacteria can sometimes spread to other parts of the body and cause infections. Haemophilus influenzae serotype B (HIB) was a major cause of meningitis in children until an effective vaccine was given to treat it. Currently, most cases of Hemophilus influenzae meningitis occur in adults in undescribed strains [40]. All antigenic serotypes can cause invasive disease, which is more commonly reported in pediatric patients. Non-capsule strains have fewer viruses and rarely cause serious infections in children [41]. Hemophilus influenzae is rare due to childhood vaccinations and possibly herd safety. Since 2013, national immunization programs have included the Hemophilus influenzae vaccine in 189 countries with about 50 percent of the world's children's coverage. However, Haemophilus influenzae is the leading cause of meningitis among unvaccinated children, especially in developing countries. Meningitis rash is more common in meningitis infections, which is now the most common cause of meningitis in some countries and often occurs with septicemia [40, 41].

Immune activation and inflammatory response in the brain

Inflammation as an important and fundamental mechanism in the field of neurological disorders is caused by various causes, but its role in changing brain's function as a result of infectious neurological diseases is unclear. Several studies have shown that eradicating pathogens within the central nervous system (CNS) may require immune responses that interfere with the function of nerve cells and communication without affecting their survival. During infectious neurological diseases, innate immune molecules such as complementary proteins and cytokines regulate synaptic flexibility and neurogenesis, while amyloid β and α-synuclein and biological markers of neurological disease play an antimicrobial role [42, 43].

The penetration of neutrophils into the scapular chamber is highly important for the secretion of pathogens, but leads to the clinical symptoms of meningitis including headache, neck stiffness (meningitis) and photophobia. These symptoms are the result of the expression of catecholamines by phagocytes exposed to bacterial products that cause mydriasis and lead to excessive light transmission to the brain and vasospasm [44, 45]. High concentrations of TH1 cytokines such as IL-1β, tumor necrosis factor (TNF) and interferon-γ (IFN-γ) in the cerebrospinal fluid of patients with infectious meningitis are also associated with cognitive impairment [46]. During bacterial meningitis, monocyte-derived macrophages play a protective role in the central nervous system, especially meningeal macrophages. However, pathogens could cause neurotoxicity through Toll-like receptors by releasing cell death signals such as oxidants or activating inflammatory components such as caspase-1 [47].

Meningitis at different ages

Meningitis occurs in all age groups, but infants have the highest risk of bacterial meningitis and meningitis, and there is another peak in adolescents and adults. Viral meningitis is more common and accounts for more than half of the cases, but bacterial meningitis is particularly important due to high mortality rate [48]. It is estimated that the average general practitioner observes one or two cases of bacterial meningitis during his or her career. The incidence of bacterial meningitis confirmed by bacterial culture in developed countries is estimated at 0.3 per 1,000 live births [49].

Mortality from bacterial meningitis in children has been reported to be 20 to 30 percent, and this rate decreases with age. Children with bacterial meningitis may have seizures or reddish-purple spots on their skin. The most common bacteria that cause meningitis in infants are gram-negative bacilli and group B strains and listeria. In infants over one month of age, Haemophilus influenzae and Neisseria meningitidis have been reported to be the most common causes of meningitis. Also, in adults, most patients were diagnosed with meningococcus and pneumococcus [50].

Bacterial meningitis is very dangerous and deadly and requires timely diagnosis, even though other types of meningitis are rare and not considered a major risk. To diagnose bacterial meningitis from the other types, spinal cord fluid culture is required, and the patient's chances of dying or other complications are high during SPF culture and response. For this reason, methods that could quickly diagnose the disease are highly needed.

Diagnosis methods

Infectious meningitis may be caused by bacterial, mycobacterial, fungal, or viral agents. In the diagnosis of meningitis, several cases of the patient's history and symptoms should be considered along with regional epidemiology and initial CSF test (protein, etc.) so that the physician could consider the possibility of disease and rationally choose additional diagnostic tests. Bacterial culture is often the main basis for diagnosis.

CT and MRI may be used as adjunctive diagnostic tests to identify meningitis, but are generally non-specific. Imaging might be helpful in cases of focal neurological defects, especially when you suspect tuberculosis or cryptococcus. In the absence of trauma, mood swings or focal neurological impairment, imaging increases the cost of health care and minimizes performance in providing a definitive diagnosis. The standard diagnostic test for cerebrospinal fluid includes white blood cell counts, total protein, and blood sugar, which are used in connection with the patient's history and epidemiology to support possible diagnoses. The total amount of protein and the number of white blood cells reflect inflammation in the cerebrospinal fluid, while a decrease in the ratio of cerebrospinal fluid glucose to blood glucose is a sign that glucose is being consumed by an active infection. These common laboratory tests may not be a perfect laboratory method, as different amounts of different diagnoses overlap but generally help the doctor focus on specific diagnoses.

Cerebrospinal fluid sampling (LP)

The most important and accurate way to correctly diagnose meningitis is to take a sample of cerebrospinal fluid. Lumbar puncture (LP) is used to take a sample and the person will not have many side effects if done correctly. This method is one of the most accurate methods of diagnosing the disease, which requires 18 to 24 hours, and for some reason, a small number of cases of bacterial meningitis can be identified with this method [51].

The CSF values of bacterial meningitis in adults are as follows. The amount of cerebrospinal fluid leukocytes is 494 / microliter, 80% neutrophil, 2.45 g / l protein and 0.36 blood sugar level. If the level of liquid sugar is low, its protein has increased and the level of its white blood cells is high, it is a sign of meningitis. The appearance of the cerebrospinal fluid itself is also an important factor in the diagnosis of meningitis. In 100% of people with the disease, the fluid is turbid. Which can occur due to increased leukocytes. Pleocytosis is also almost always present in most patients, and the number of white blood cells varies from 100 to 1000 cells per microliter [2, 51].

Based on the studies of cerebrospinal fluid bacteria could be detected by the presence of inflammatory cells, bacterial antigens and bacterial culture in the cerebrospinal fluid sample. In the early stages of the disease, headache, mild fever, and some degree of mood swings and forgetfulness occur in young patients and high mortality in adult patients. Examination of the cerebrospinal fluid in these patients showed that the single-

nucleated white blood cells had increased sharply, the sugar had decreased markedly, and the protein had increased [2].

Risk Factor Score

Symptoms of meningitis may have other causes. Many clinical signs and symptoms and laboratory tests of blood and cerebrospinal fluid in meningitis are examined, but none of these are completely different in terms of the presence or absence of bacterial meningitis. Because delaying the diagnosis and treatment of bacterial meningitis makes the treatment more difficult, doctors have little amount of time to perform LP and start antibiotic treatment of bacterial meningitis in children. On the other hand, performing LP and experimental treatment of these children may be considered somewhat unnecessary later [52]. The two main problems we face are that to ensure the presence or absence of bacterial meningitis, which makes it necessary to perform LP, and on the other hand, based on direct examination of cerebrospinal fluid data, antibiotics must be used until cultivation is available [53].

There is no doubt that bacterial meningitis is a dangerous disease for humans. Clinical deterioration in the disease can occur rapidly and is often difficult to predict. A risk ranking can be useful in assessing the risk and subsequent management of patients [54]. Researchers are trying to identify bacterial meningitis predictors to estimate the risk of the disease and to avoid unnecessary testing by correctly identifying people who need immediate treatment, as well as reducing the extra cost on families and communities. There are different rules for using this tool. Some of them include complex multivariate models that are needed to perform on computers, and the doctor cannot easily diagnose the disease with their help. Others use a simple scoring system that scores definite signs and symptoms which is more appropriate for use in the treatment process [55, 54].

In one study, the number of leukocytes, cognitive impairment and infection with Streptococcus pneumoniae were collected as prognostic factors in adults with bacterial meningitis. The aim of this study was to extract and validate a simple scoring system for predicting meningitis. This ranking makes it clear that patients with bacterial meningitis can be classified in the early stages. The results confirmed that the model could not completely differentiate between patients with meningitis and healthy [55].

The bacterial meningitis score is a rule for the clinical prognosis of children with CSF pleocytosis who have a very low risk of bacterial meningitis. Bacterial meningitis scores for children with CSF pleocytosis who have not undergone neurosurgery, have not been associated with any disease, and no antibiotic pre-treatment has been achieved in 72 hours after the LP, were very low [56]. Those who did not have any high-risk laboratory predictions were classified as having very low risk for bacterial meningitis. In a study of children, the system could finely classify bacterial meningitis as well, but with very few features. According to the study, a small minority of infants with CSF pleocytosis were classified as very low-risk due to their bacterial meningitis score. Careful supportive decision-making tools for children with CSF pleocytosis with a risk of bacterial meningitis close to zero using clinical and laboratory parameters were readily available at the time of clinical presentation and could guide physicians, also limit unnecessary hospitalizations and long-term use of antibiotics [56, 55].

New methods for classifying risk are needed to accurately identify infants with bacterial meningitis from low-risk individuals. Neither clinical grading algorithms nor complete blood counts are suitable for this purpose, and they do not accurately identify infants at low risk for bacterial infections, including bacterial meningitis [57].

Oostenbrink rules are potentially very useful to physicians because they are simple and could help us make decisions about LP and treat patients experimentally with antibiotics (Table 1). A Oostenbrink rules based study of 226 children in four Dutch hospitals found that two out of 25 children with meningitis had a grade point average of less than 9.5. One in two children had symptoms of meningitis and prolonged seizures. None of the other 205 children with a score of less than 8.5 had bacterial meningitis. 13% had the disease with a score between 8.5 and 14.9. In 52%, the disease was observed with a score of 15.0 to 19.9; Also, 87% of people with a score of 20.0 or more had meningitis. Using this law, the number of hospitalizations was reduced by 33% in the hospital, and unnecessary LPs were prevented from occurring in 5% of individuals, and additional financial costs to the individual and the community were significantly reduced [58].

Table 1. Oostenbrink rules for predicting the risk of bacterial meningitis in children with meningitis symptoms

Risk factor	Score
Patients age The duration of the patient's problem	1month-15years 1.0 per day (10 maximum)
History of vomiting	2.0
Cyanosis	6.5
Disturbed consciousness	8.0
Meningeal irritation *	7.5
Petechiae	4.0
Serum concentration of reactive protein C (mg / l or deciliters)	
<5.0 (50)	0
5.0-9.9(50-99)	0.5
10.0-14.9 (100-149)	1.0
15.0-19.9 (150-199)	1.5
>20.0 (200)	2.0
	total

Brudzinski's symptom (passive bending of the neck towards the chest causes the knees and hips to bend); Kernig's sign (stretching of the lower leg when the thigh is bent toward the trunk at a 90-degree angle is painfully limited); Tripod position (legs bent and arms stretched at the elbow) while sitting. Or neck stiffness, irritability while moving the head or legs, as well as prominent Fontanel may be seen in children under one year of age.

The minimum age according to Stenbrink's criteria should be more than one month, and children whose score is 8.5 or higher should be LP. Nigrovic's law is preferable to Oostenbrink because it is easier to use and 66 percent more specific (Table 2); A study of 12 children with a score of less than 8.5 using Stenbrink's law found bacterial meningitis, and their disease was identified by Nigrovic's law [59].

Table 2. Nigrovic scoring rules for identifying people with meningitis

Risk factor			
Gram-positive staining of cerebrospinal fluid			
Level of cerebrospinal fluid protein< 80 mg / dL (800 mg / L)			
Total number of side neutrophils<10,000 cells per cubic millimeter (109 x 10 liters)			
Seizure			
Total amount of cerebrospinal fluid neutrophils< 1000 cells per cubic millimeter (1×10^9 per liter)			
Bacterial meningitis samples / total patients (%)			
Number of risk factors	2002 Nigrovic	6 200Nigrovic	Nigrovic 2007
0	0.144 (0)	0.86 (0)	2.1, 714 (0.1)
1or moe	38.90 (42)	20.65 (31)	119.1 , 189 (10)

CONCLUSION AND PERSPECTIVE

Meningitis, if left untreated, can lead to serious complications and even death. Therefore, early and accurate diagnosis is one of the research priorities of this disease. There are many methods available, such as examining the patient's clinical symptoms, performing MRI and CT scans, biochemical blood tests, and examining the cerebrospinal fluid. The most appropriate method available is to examine the cerebrospinal fluid, which requires a hole in the patient's back. Researchers have used scoring methods to quickly identify patients, prevent unnecessary treatment or performing LP. It could be said that Ningrovic and Oostenbrink laws have the best balance between validity and ease of use. These rules should not be completely trusted. For example, seizures are relatively rare and do not meet statistical criteria for entering the Oostenbrink law. However, any child with suspected meningitis and seizures should have an LP. All suspected children with meningitis must be closely monitored, whether LP or experimental treatment [60].

In recent years, penicillin, chloramphenicol, and sulfadiazine antibiotics have been used to treat meningitis. With the introduction of stronger antibiotics, studies have been conducted to change traditional drug regimens in use and replace them with newer drug regimens that have been more effective and safer. A 1991 study by Nabil et al., found that ampicillin and third-generation antibiotics such as ceftriaxone cephalosporins were highly effective in treating acute bacterial meningitis [61]. It should be noted that these medications do not apply to meningitis in immunocompromised individuals, neonatal meningitis or tuberculous meningitis. Unfortunately, due to the increase in the uncontrolled use of antibiotics, the emerging phenomenon of antibiotic resistance against this disease is also observed.

Hopfully by using appropriate methods and approaches, meningitis will be identified quickly and correctly and will be effectively treated over time to prevent side effects and death, as well as reduce additional costs on families and the community.

REFERENCES

1. Mandell GL, B.J., Dolin R, Tunkel AR, Scheld WM, Acute meningitis. Principles and practice of infectious dis, 2005, Elsevier: Philadelphia. p. 1083-1119.
2. Roos KL, T.K., Kasper DL, Braunwald E, Fauci AS, Longo DL, Jameson L, Harrison's internal medicine, 2004, McGraw-Hill profiessional: New York:. p. 2471-2490.
3. Saravolatz LD, M.O., Vander-Velde N, Pawlak J, Berlin B, Broad- range bacterial Polymeras chain reaction for early detection of bacterial meningitis. Clin Infect Dis, 2003. 36(1): p. 40-5.
4. Alborzi A, V.F., Karimi A, Azemodeh M, Labaf-Qasemi R, Kadivar MR, et al, Etiological agents, prevalence and complications of children meningitis in 24 month in Shiraz and Tehran. Trop and Infect Dis J 2002. 7(18): p. 26-31.
5. G, C., Bacterial Meningitis, In: Nelson texet book of pediatrics edited by Behrman RE, Kliegman RM, Jenson HB, 2000, Sunders: Philadelphia. p. 751-757.
6. Mel'nikova EV, S.O., Borisova MN, et al, Characteristics of the strategy of intensive care of unconscious children. Anesteziol Reanimatol, 2000. 1: p. 36-38
7. van de Beek D, d.G.J., Tunkel AR, Wijdicks EF, Community-acquired bacterial meningitis in adults. N Engl J Med, 2006. 354: p. 44 –53.
8. Sinclair D, P.M., Jacob JT, Greenwood B, The epidemiology of meningococcal disease in India. Trop Med Int Health, 2010. 15(12): p. 1421-35.
9. P G Davey, J.K.C., I C McManus, B Mahood, M H Snow, and A M Geddes, Bacterial meningitis--ten years experience. J Hyg (Lond), 1982 88(3): p. 383–401.
10. Heydari et al. Epidemiology of patients with acute meningitis and meningoencephalitisMedical Journal of MashhadUniversity of Medical Sciences.2006. Vol.49, No: 91, P: 185 - 190.
11. Shankar P, M.N., Mohan KK, Prasad K, Behari M, Shriniwas , Ahuja GK, Rapid diagnosis of tuberculous meningitis by polymerase chain reaction. Lancet 1991 337: p. 5-7.
12. Molavi A, L.J., Tuberculous meningitis. Med Clin North Am, 1985 69(2): p. 315-31.
13. Thwaites GE, C.M., Chau TT, Dung NT, Campbell JI, Phu NH, Hien TT, White NJ, Farrar JJ. , Comparison of conventional bacteriology with nucleic acid amplification (amplified mycobacterium direct test) for diagnosis of tuberculous meningitis before and after inception of antituberculosis chemotherapy. J Clin Microbiol, 2004 42(3): p. 996-1002.
14. Caws MS, W.M., Clough C, Drobniewski F, Role of IS6110-target PCR, culture, biochemical, clinical and immunological criteria for diagnosis of Tuberculous meningitis. J Clin Microbiol, 2000 38(9): p. 3150-5.
15. Kastenbauer S, a.H.W.P., Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in a series of 87 cases. Brain 2003. 126: p. 1015–1025.
16. Weisfelt M, D.v.d.B., L Spanjaard, J B Reitsma, and J de Gans, Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. Lancet Neurology, 2006. 5: p. 123–129
17. Bogaert D, E.M., Timmers-Reker AJ, et al, Pneumococcal carriage in children in The Netherlands: a molecular epidemiological study. Clin Microbiol, 2001 39(9): p. 33-16 .20
18. Ihekweazu C, B.M., Wilson D, Oliver I, Dance D, George R, Pebody R, Outbreaks of serious pneumococcal disease in closed settings in the post-antibiotic era: a systematic review. J Infect, 2010 61(1): p. 21-7

19. DM, M., Infections caused byStreptococcus pneumoniae: clinical spectrum, pathogenesis, immunity, and treatment. Clin Infect Dis, 1992 14(4): p. 801-7.
20. Weisfelt M, v.d.B.D., Spanjaard L, de Gans J, J Hosp, Nosocomial bacterial meningitis in adults: a prospective series of 50 cases. Infect, 2007 66(1): p. 71-8.
21. Orihuela CJ, M.J., Thornton J, et al, Laminin receptor initiates bacterial contact with the blood brain barrier in experimental meningitis models. J Clin Invest, 2009 119(6): p. 1638-46.
22. Chang CJ, C.W., Huang LT, Huang SC, et al Bacterial meningitis in infants: the epidemiology, clinical features, and prognostic factors. Brain Dev, 2004. 26: p. 168–175.
23. Dietzman DE, F.G., Schoenknecht FD, Neonatal Escherichia coli septicemia--bacterial counts in blood. J Pediatr .1974 , :85p. 128–130.
24. Cherubin C, M.S., Sierra MF, Becker S, Listeria and gram-negative bacillary meningitis in New York City, 1972–1979 Frequent causes of meningitis in adults. Am J Med 1981 71 (2): p. 199-209.
25. Yang TM, L.C., Huang CR, et al, Clinical characteristics of adult Escherichia coli meningitis. Jpn J Infect Dis, 2005 58(3): p. 168-70
26. KS, K., Current concepts on the pathogenesis of E. coli meningitis; implications for prevention and therapy. Curr Opin Infect Dis, 2012. 25: p. 2.278–73
27. KS, K., Acute bacterial meningitis in infants and children. Lancet Infect Dis, 2010. 10: p. 32–42.
28. KS, K., How pathogens penetrate the blood-brain barrier. Microbe, 2014. 9: p. 487–492.
29. Sarff LD, M.G.J., Schiffer MS, et al Epidemiologyof Escherichia coli K1 in healthy and diseased newborns. Lancet, 1975. 1: p. 1099–1104.
30. Mangi R, Q.R., Andriole V T.Gram-negative bacillary meningitis. Am J Med, 1975 59(6): p. 829-36.
31. Lu CH, C., WN Chuang YC, Chang HW, The prognostic factors ofadult Gramnegative bacillary meningitis. J Hosp Infect 1998 40 (1): p. 27-34.
32. A, W., Ueber die Aetiologie der akuten meningitis cerebrospinalis. Fortschr Med, 1887. 5: p. 573.
33. Rosenstein NE, P.B., Stephens DS, et al, Meningococcal disease. N EnglJ Med, 2001. 344: p. 1378–88.
34. Schoenback E, P.J., The sensitivity of meningococci to sulfadiazine. Am J Hyg, 1948. 47: p. 177–86.
35. Artenstein MS, G.R., Zimmerly JG, et al, Prevention of meningococcal disease by group C polysaccharide vaccine. N Engl J Med, 1970. 282: p. 417–20.
36. Sigurdardottir B, B.O., Jonsdottir KE, et al, Acute bacterial meningitis in adults: a 20-year overview. Arch Intern Med, 1997. 157 p. 425-30.
37. Mylonakis E, H.E., Calderwood SB, Central nervous system infection with Listeria monocytogenes: 33 years of experience at a general hospital and review of 776 episodes from the literature. Medicine Baltimore, 1998. 77: p. 313-36.
38. Attia J, H.R., Cook DJ, et al, The rational clinical examination: does this adult patient haveacute meningitis? JAMA, 1999. 282: p. 175-81.
39. van de Beek D, d.G.J., Spanjaard L, et al, Antibiotic guidelines and antibiotic use in adults: bacterial meningitis in the Netherlands. J Antimicrob Chemother, 2002. 49: p. 661-6.
40. Brouwer MC, T.A., vande Beek D, Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev, 2010 23(3): p. 467-92.
41. M, K., Haemophilus. In: Murray, in Manual of clinical microbiology2007, American Society for Microbiology: Washington, DC. p. 636–648
42. Kumar DK, C.S., Washicosky KJ, et al Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med, 2016 8(340): p. 340ra72.
43. Beatman EL, M.A., Shives KD, et al, Alpha-Synuclein Expression Restricts RNA Viral Infections in the Brain. J Virol, 2015 90(6): p. 2767-82
44. Flierl MA, R.D., Nadeau BA, Chen AJ, et al Phagocyte-derived catecholamines enhance acute inflammatory injury. Nature, 2007 449(7163): p. 721-5.
45. Aydin N, K.D., Keles S, Ondas O, Aydin MD, Baykal O, Gundogdu B, An experimental study of the neurophysical mechanisms of photophobia induced by subarachnoid hemorrhage. Neurosci Lett, 2016 630: p. 93-100.
46. Hikita N, S.T., Yamashita K, Iritani N, AataM, Ogura H, Shintaku H, Relationship between Severity of Aseptic Meningitis and Cerebrospinal Fluid Cytokine Levels. Osaka City Med J, 2015 61(2): p. 63-71.
47. Gerber J, N.R., Mechanisms of injury in bacterial meningitis. Curr Opin Neurol, 2010 23(3): p.8-312 .
48. Griffiths MJ, M.F., Solomon T, Management of acute meningitis. Clin Med, 2018 18(2): p. 164-169.
49. Ku LC, B.K., Cohen-Wolkowiez M, Bacterial meningitis in infants. Clin Perinatol, 2015 42(1): p. 29-45.
50. Wilder-Smith A, G.K., Barkham T, Paton NS, outbreak of neisseria meningitides serogroup W135: Estimate of the attack rate in a defind population and risk of invasion developing in carrier Clin INF Disease, 2003. 36: p. 679-683
51. Gooya MM, Z.S., Shirazi MR, and Nahid P, Information and Statistics of Contagous Diseases in Iran (1977 – 2002). Seda publication, 2004 1: p. 133-210.
52. Valmari P, P.H., Ruuskanen O, Korvenranta H, Childhood bacterial meningitis: Initial symptoms and signs related to age, and reasons for consulting a physician .Eur J Pediatr 1987. 146: p. 515–518.
53. Feigin RD, M.J., GH, Klein JO, Diagnosis and management of meningitis. Pediatr Infect Dis J, 1992. 11: p. 785–814.
54. Aronin SI, P.P., Quagliarello VJ. C, ommunity-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med, 1998. 129: p. 862– 869.
55. Martijn Weisfelt, D.v.d.B., Lodewijk Spanjaard, Johannes B. Reitsma, and Jan de Gans, A Risk Score for Unfavorable Outcome in Adults with Bacterial Meningitis. Ann Neurol 2008. 63: p. 90–97.
56. Nigrovic LE, K.N., Macias CG, et al, Pediatric Emergency Medicine Collaborative Research Committee, American Academy of Pediatrics. Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. JAMA 2007. 297: p. 52–60.
57. Cruz AT, M.P., Bonsu BK, et al, Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. JAMA Pediatr, 2017. 171: p. e172927.
58. Oostenbrink R, M.K., Derksen-Lubsen AG, Grobbee DE, Moll HA, A diagnostic decision rule for management of children with meningeal signs. EurJ Epidemiol 2004. 19: p. 109–16.
59. Nigrovic LE, K.N., Macias CG, Cannavino CR, Moro-Sutherland DM, Schremmer RD, et al, Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. JAMA, 2007. 297: p. 52–60.
60. EBELL, M.H., Predicting the Likelihood of Bacterial Meningitis in Children. Am Fam Physician, 2007 15(4): p. 533-535.
61. Nabil I. Girgis, M.E.K., Zoheir Farid and John E. Sippel, A review of the treatment of bacterial meningitis. TROPICAL MEDICINE AND HYGIENE, 1991. 85: p. 1-3